Current-Controlled Electrical Point-Source Stimulation of Embryonic Stem Cells.

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Public Summary:

Scientific Abstract:
Stem cell therapy is emerging as a promising clinical approach for myocardial repair. However, the interactions between the graft and host, resulting in inconsistent levels of integration, remain largely unknown. In particular, the influence of electrical activity of the surrounding host tissue on graft differentiation and integration is poorly understood. In order to study this influence under controlled conditions, an in vitro system was developed. Electrical pacing of differentiating murine embryonic stem (ES) cells was performed at physiologically relevant levels through direct contact with microelectrodes, simulating the local activation resulting from contact with surrounding electroactive tissue. Cells stimulated with a charged balanced voltage-controlled current source for up to 4 days were analyzed for cardiac and ES cell gene expression using real-time PCR, immunofluorescent imaging, and genome microarray analysis. Results varied between ES cells from three progressive differentiation stages and stimulation amplitudes (nine conditions), indicating a high sensitivity to electrical pacing. Conditions that maximally encouraged cardiomyocyte differentiation were found with Day 7 EBs stimulated at 30 microA. The resulting gene expression included a sixfold increase in troponin-T and a twofold increase in beta-MHCwithout increasing ES cell proliferation marker Nanog. Subsequent genome microarray analysis revealed broad transcriptome changes after pacing. Concurrent to upregulation of mature gene programs including cardiovascular, neurological, and musculoskeletal systems is the apparent downregulation of important self-renewal and pluripotency genes. Overall, a robust system capable of long-term stimulation of ES cells is demonstrated, and specific conditions are outlined that most encourage cardiomyocyte differentiation.